Claims 13 (Amended). A process for preparing a pharmaceutical composition, in which ~~a protein~~ having a molecular weight of about 24 kd [according to any one of claims 1 to 3], or a functionally equivalent variant or fragment thereof, and capable of specifically binding to a protein of hepatitis C virus, is combined [brought into association] with a pharmaceutical acceptable carrier.

Claim 14 (Amended). A protein having a molecular weight of about 24 kd [according to any one of claims 1 to 3], or a functionally equivalent variant or fragment thereof, for use as a pharmaceutical.

Claim 17 (Amended). A diagnostic kit comprising a [the] protein having a molecular weight of about 24 kd [according to any one of claims 1 to 3], or a functionally equivalent variant or fragment thereof, and capable of specifically binding to ~~a protein~~ of hepatitis C virus.

Remarks

Status of the Claims

Claims 1-20 were pending in the application. Claims 16 and 18-20 were withdrawn from consideration. Claims 1-15 and 17 were rejected. Claims 1, 5, 15, 16 and 18-20 have been canceled herein, without prejudice. Claims 2-4, 6-14 and 17 are currently pending. Claims 2-4, 6-14 and 17 have been amended herein.

Summary of the Amendments

Claim 2 has been amended to depend from claim 4. Support is found throughout the specification as filed, and in claim 4 of the application as originally filed.

Claim 3 has been amended to depend from claim 4. Support is found throughout the specification as filed, and in claim 4 of the application as originally filed.

Claim 4 has been amended to be independent and incorporate the subject matter of canceled claim 1 therein. Claim 4 has been further amended to recite "obtaining a membrane preparation from cells" rather than "the step of culturing cells." Support is found throughout the specification as filed, and in claim 4 of the application as originally filed. No new matter is added.

Claims 6-10 have been amended to eliminate improper multiple dependency.

Claims 7-10 have been further amended to define more clearly the subject matter of the claims. The terms "preparing," "subjected to," and "subjecting" have been replaced by the terms "purified by," "obtaining" or "precipitating." Support is found throughout the specification as filed, and in each of the claims of the application as originally filed. No new matter is added.

Claim 7 has been further amended to recite "at between 33 and 50% saturation." Support is found throughout the specification as filed, particularly page 31, lines 8-10, and in claim 7 of the application as originally filed. No new matter is added.

Claims 11-13 and 17 have been amended to eliminate improper multiple dependency. Claims 11-13 and 17 have been further amended to recite "a protein having a molecular weight of about 24kd . . . and capable of specifically binding a protein of hepatitis C virus" rather than "a protein according to any one of claims 1 to 3." Support is found throughout

the specification as filed, and in claims 11-13 and 17 of the application as originally filed. No new matter is added.

Claim 11 has been amended to recite "a patient infected with HCV" rather than "an infection of HCV." Support is found throughout the specification as filed, and in claim 11 of the application as originally filed. No new matter is added.

Claim 12 has been amended to replace "a protein according to any one of claims 1 or 3 or a functionally equivalent variant or fragment thereof, optionally as a pharmaceutical salt" with "a protein having a molecular weight of about 24kd, or a functionally equivalent variant or fragment thereof, and capable of specifically binding a protein of hepatitis C virus." Support is found throughout the specification as filed, and in claim 12 of the application as originally filed. No new matter is added.

Claim 13 has been amended to replace "brought into association" with "combined." Support is found throughout the specification as filed, and in claim 13 of the application as originally filed. No new matter is added.

Claim 14 has been amended to be independent and incorporate the subject matter of canceled claim 1 therein. Support is found throughout the specification as filed, and in claim 14 of the application as originally filed. No new matter is added.

In view of the foregoing amendments and arguments that follow, Applicant respectfully requests withdrawal of all rejections upon reconsideration.

Preliminarily, in view of voluminous nature of reference C3, Applicant has not enclosed a copy with the Supplemental Information Disclosure Statement. However, the reference

simply provides background information and, regardless, the Examiner should have access to it. If not, Applicant will endeavor to supply a copy at the Examiner's request.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 1-15, and 17 were rejected under 35 U.S.C. § 112, second paragraph, as being allegedly indefinite for failing to particularly point out and distinctly claim the subject which the applicant regards as his invention. Claims 1, 5 and 15 have been canceled. Applicant respectfully traverses this rejection as applied to the remaining claims.

Claims 2-4, 11-15, and 17 were rejected under § 112, second paragraph, because, according to the rejection, it was allegedly unclear whether the phrase "functionally equivalent variant or fragment thereof" is intended to modify the 24kd protein or the HCV protein. This rejection as to claims 2-4, 11-114 and 17 has been obviated by amendment. Applicant respectfully requests that the rejection of these claims, under § 112, second paragraph, be withdrawn.

Claims 2-4, 11-15, and 17 were further rejected as the specification allegedly fails to teach the metes and bounds of "functionally equivalent variant." The rejection maintains that it is unclear what function is to be considered in determining equivalency and how proteins can vary and still remain functional equivalents. The rejection maintains that the term "fragment" is similarly indefinite because the specification fails to set forth the metes and bounds of the disclosed fragment's length. Applicant respectfully traverses this rejection, and submits that claims 2-4, 11-15, and 17 are not indefinite as to the variants and fragments disclosed therein.

The specification sets forth ample guidance for a person of ordinary skill to

understand the function to be considered for the claimed variants and fragments. Variants and fragments of the claimed invention are understood to retain the function of binding to HCV. For instance, the specification at page 3, lines 33-31 sets forth guidance as to the characteristics of the claimed variant, stating that the 24kd protein can be "modified, provided that it retains the functional characteristic of at least binding to E2 protein of HCV." In addition, the variant "may include modifications of the amino acid sequence involving one or more insertions, deletions or replaced amino acids," or "may, for example, be truncated by the removal of a functional part of the transmembrane domain" (page 3, line 36 - page 4, line 1). In every case, the variant retains a functional domain, derived or modified from the 24kd protein, that binds HCV.

Similarly, the fragments of the present invention also retain the function of binding to HCV. Thus, the length of the fragment, which the Examiner emphasizes as an indefinite aspect of the invention, is clearly the minimum that binds to HCV. The Examiner takes her reading of "fragment" to its logical extreme, pointing out that a fragment of as little as a single amino acid may be encompassed. Applicant respectfully submits that one of ordinary skill in the art would not consider a single amino acid to satisfy the "functionally equivalent" limitation of the claims. If the Examiner maintains this position, she is requested to provide evidence in the form of an affidavit or reference pursuant to 37 C.F.R. § 1.104(d)(2). Applicant respectfully requests that the rejections of these claims, under § 112, second paragraph, be withdrawn.

Claim 2 was further rejected under § 112, second paragraph. It was alleged that reciting the term "functionally" twice renders the claim indefinite. This rejection seems untenable. The term "functionally" is not used inconsistently; it is used to modify two different words.

Applicant respectfully requests that the rejection of claim 2, under § 112, second paragraph, be withdrawn.

Claim 4 was further rejected under § 112, second paragraph, because, according to the rejection, it is allegedly unclear whether the phrase "cell preparation" is intended to recite a different population from the disclosed cultured cells. This rejection has been obviated by amendment. Applicant respectfully requests that the rejection of claim 4, under § 112, second paragraph, be withdrawn.

Claim 5 was rejected under § 112, second paragraph, because, according to the rejection, it is allegedly unclear whether the phrase "cell preparation" is intended to recite a different population from the disclosed cultured cells. Claim 5 has been canceled. The rejection is hereby rendered moot.

Claims 6 and 10 were rejected under § 112, because, according to the rejection, the metes and bounds of "hyperexpression" are allegedly not defined in the specification. This rejection has been obviated by amendment. Applicant respectfully requests that the rejection of claims 6 and 10, under § 112, second paragraph, be withdrawn.

Claims 7-9 were rejected under § 112 because, according to the rejection, the claimed process allegedly fails to set forth any active steps. In particular, the rejection maintains that claim 7 is indefinite because the phrase "subjected to" does not describe an active step. Further, the rejection maintains that claims 8 and 9 are indefinite because the term "involves" is not an active step. This rejection has been obviated by amendment. Applicant respectfully requests that the rejection of claims 7-9, under § 112, second paragraph, be withdrawn.

Claim 8 was further rejected under § 112 because, allegedly, the phrase "at least one step of hydrophobic interaction chromatography" is indefinite since it 1) fails to teach the steps of hydrophobic interaction chromatography; and 2) it is unclear whether "at least one step" is intended to encompass a single step practiced one or more times, or plural steps, one of which is to be incorporated into the claimed process. The applicant respectfully disagrees, and urges that the specification adequately sets forth the steps of hydrophobic interaction chromatography.

The steps of hydrophobic interaction chromatography are well known by those of ordinary skill in the art (*See* Gooding, (1995), *Molecular Biology and Biotechnology*, 417-420). Further, the applicant's specification sets forth an example detailing the steps of hydrophobic interaction chromatography (page 31, line 21 - page 32, line 10).

The latter ground of rejection has been obviated by amendment. Claim 8 recites that at least one hydrophobic interaction chromatography procedure is to be performed. Applicant respectfully requests that the rejection of claim 8, under § 112, second paragraph, be withdrawn.

Claim 9 was further rejected under § 112, because, according to the Examiner, the phrase "one step of acetone precipitation" is allegedly indefinite for 1) failing to teach the steps of acetone precipitation; and 2) failing to disclose where this step fits into the claimed process.

The steps of acetone precipitation are well within the knowledge of one of ordinary skill the art (*see e.g.,* U.S. Patent Nos. 5,965,414, and 4,958,690). Further, applicant's specification sets forth an example detailing the steps of acetone precipitation (page 32, lines 12-22).

The latter ground of rejection has been obviated by amendment. Claim 9 recites that at least one acetone precipitation procedure is conducted. One of ordinary skill understands

that acetone precipitation is associated with step ii) of the claimed process, and, therefore, the Examiner's concern regarding where the step "fits" is misplaced. Applicant respectfully requests that the rejection of claim 8, under § 112, second paragraph, be withdrawn.

Claim 10 was further rejected under § 112, second paragraph because, it was pointed out, the phrase "wherein comprising" is improper syntax. Claim 10 has been amended to correct this syntactical error.

Claim 10 was further rejected under § 112 because, according to the rejection, the phrases "preparing a . . . preparation" and "subjecting to" allegedly fail to disclose active steps. Without conceding its correctness, this rejection has been obviated by amendment.

Claim 10 was further rejected under § 112, second paragraph, because, according to the rejection, the term "resuspending" is allegedly indefinite. Applicant respectfully traverses this rejection, and submits that claim 10 is definite as to the use of "resuspending."

Applicant respectfully submits that a person of ordinary skill in the art would not consider the step of "resuspending" to mean that the precipitate is to be suspended back into the original cell preparation, as suggested by the Examiner. A person of ordinary skill would interpret "resuspending" to mean that the precipitate is to be suspended in solution again, without requiring a particular solution. There is no teaching or suggestion in the claims or the specification that ascribes the Examiner's meaning to "resuspending," and the rejection fails to cite any indications to the contrary.

Applicant respectfully requests that the rejection of claim 10, under § 112, second paragraph, be withdrawn.

Claim 11 was further rejected under § 112, because, according to the rejection, the phrase "method for treating an infection of HCV" is allegedly indefinite as being susceptible of an obviously unintended interpretation. Claim 11 has been amended to obviate the alleged ambiguity. Applicant respectfully requests that the rejection of claim 11, under § 112, second paragraph, be withdrawn.

Claim 12 was further rejected under § 112, second paragraph, because, it was argued, "optionally as a pharmaceutically acceptable salt" is allegedly indefinite. This rejection has been obviated by amendment. Applicant respectfully requests that the rejection of claim 12, under § 112, second paragraph, be withdrawn.

Claim 13 was further rejected under § 112 because, according to the rejection, "brought into association with" is allegedly indefinite. This rejection has been obviated by amendment. Applicant respectfully requests that the rejection of claim 13, under § 112, second paragraph, be withdrawn.

Rejection Under 35 U.S.C. § 101

Claim 15 was rejected under 35 U.S.C. § 101 because, according to the rejection, the claim recites a use without setting forth any steps involved in the recited process. Claim 15 has been canceled. The rejection is hereby rendered moot.

Rejection Under U.S.C. § 112, First Paragraph

Claim 1-15 and 17 were rejected under 35 U.S.C. § 112, first paragraph, as

containing subject matter which allegedly is not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 1, 5 and 15 have been canceled. Applicant respectfully traverses this rejection as applied to the remaining claims.

The § 112, first paragraph, rejection is divided, essentially, into two parts. The first part is directed to claims 1-4, 11-15 and 17, and appears to be based solely on arguments made regarding the second paragraph rejections, *supra*. Indeed, the Examiner merely reiterates and/or refers to arguments made with regard to indefiniteness in maintaining this part of the enablement rejection. In view of the foregoing arguments and amendments, applicant respectfully submits that these rejections have been obviated and requests that they be withdrawn.

In the second part, claims 11-15 were rejected under § 112, first paragraph, because, according to the rejection, neither the applicant's specification, nor the art, teaches that proteins which bind to HCV have any current therapeutic application for treatment of HCV infection. The rejection cites Rice, *Hepatology*, (1999), 3:990-992, which purportedly teaches that E2 binds human CD81. According to the rejection, Rice teaches that although the binding of HCV E2 to CD81 offers clues as to how HCV attaches to cells, it does not prove that CD81 is the cellular receptor for HCV. The rejection also maintains that although Rice teaches that antibodies capable of blocking E2 might also be used to neutralize HCV infectivity *in vivo*, Rice does not teach how compositions could be made, what neutralizing antibodies would be effective, or how these antibodies could be administered. The rejection concludes that the applicant's disclosure must provide working examples describing blocking of HCV attachment to susceptible cells by

administering the claimed protein *in vivo*. The Examiner argues that the applicant has not provided such examples, and, therefore, the claimed subject matter is not enabled. Applicant respectfully traverses the rejection and submits that claim 11-14 are fully enabled by the specification.

In support of the rejection, the Examiner maintains that Rice teaches that any potential therapeutic application of CD81 will depend on many unknowns. Rice states, however, that the therapeutic potential of CD81 is dependent upon whether the E2-CD81 interaction is critical for HCV infection (page 990). Rice suggests that evidence of this criticality could come from epidemiological studies, where it can be determined, for example, whether individuals with a defective CD81 allele are resistant to HCV.

Applicant's specification amply demonstrates that the 24kd protein is critical for HCV infection. For example, applicant describes analyzing various cell types, from various species, using FACscan and Western blot for the presence of HCV receptor (page 23, line 28 - page 24, line 18). The result of these studies demonstrate that the species distribution of the 24kd protein matches that of HCV infection susceptibility, *i.e.*, species resistant to infection do not have the 24 kd protein. Applicant also demonstrates that the 24kd protein is a transmembrane protein, suggesting that it is a cellular receptor (page 3, lines 21-23; page 23, line 28 - page 26, line 32, of the application as filed). These results support the conclusion reached by applicant: that the 24kd protein is critical to HCV infection (page 2, line 38 - page 3, line 2, of the application as filed).

In further support of the rejection, the Examiner also maintains that the art --Rice in particular-- does not teach how neutralizing antibodies are made or utilized *in vivo*. However, applicant does not claim neutralizing antibodies, and, therefore, the Examiner's reference to the

antibody of Rice with respect to enablement is irrelevant.

Applicant respectfully requests that the rejection of claims 11-14, under § 112, first paragraph, be withdrawn.

Rejections Under 35 U.S.C. § 102

Claim 17 was rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Rosa et al. However, Rosa et al. was published after the priority date of the present application. Since the priority document of the present application (GB 9517926) corresponds in content to the disclosure of the present application, the present claims are entitled to the claimed priority date. Accordingly, this document is not relevant to the patentability of the claimed subject matter. Applicant requests that this rejection be withdrawn.

Claims 1 and 17 were rejected under § 102(b) over Mehta et al. Claim 1 has been canceled. Applicant respectfully traverses this rejection, and submits that claim 17 are not anticipated by Mehta et al.

Anticipation under § 102 requires that each element as found in the claims of the applicant's invention be disclosed by Mehta et al. *In re Paulsen*, 30 F.3d 1475 (Fed. Cir. 1994). Because, *inter alia*, the Examiner lends an erroneous interpretation to the applicant's claim term "variant," the Examiner is mistaken that Mehta et al. anticipates applicant's invention.

"Variant," as used by the applicant, refers to the 24kd protein and, thus, does not encompass any and all proteins that bind HCV, as mistakenly asserted by the Examiner. The specification states that "the 24kd protein may be modified chemically to introduce one or more

chemical modifications to the amino acid structure" (page 3, lines 34-36). Moreover, variants of the invention "include modifications of the amino acid sequence involving one or more insertions, deletions or replaced amino acids" (*id.* At lines 36-38). Antibodies are generally about 140kd in size. *See Immunology Immunopathology and Immunity*, Stewart Sell, ed., (4th ed. 1987), pp. 85-115 (copy attached). The applicant surmises that the Examiner's rejection is specifically drawn to the functionally equivalent variants, since the Examiner does not contend that the antibodies are 24kd. Applicant respectfully submits that a person of ordinary skill in the art, reading applicant's invention, however, would not consider a variant of a 24kd protein to include monoclonal antibodies. Applicant respectfully requests that this rejection be withdrawn.

Rejection Under 35 U.S.C. § 103

Claims 1 and 17 was rejected under § 103(a) as allegedly obvious over Rosa et al. As discussed above, because Rosa et al. was published after the priority date of the present application, Rosa et al. is not relevant to the patentability of the claimed subject matter. Claim 1 has been canceled. Applicant respectfully requests that the rejection of claim 17, under § 103, be withdrawn.

Claim 17 was rejected under § 103(a) as allegedly obvious over Mehta et al. The Examiner relies on the same argument in rejecting claim 17 under § 103 as the argument made regarding the § 102 rejection. Applicant respectfully disagrees and urges that claim 17 is not obvious over Mehta et al.

Obviousness is based on a determination of: 1) the scope and content of the prior

art; 2) the level of ordinary skill in the art; 3) the differences between the claimed invention and the prior art; and 4) objective evidence of nonobviousness. *Robotic Vision Sys., Inc. v. View Engineering Inc.*, 51 U.S.P.Q.2d 1948, 1953 (Fed. Cir. 1999).

The monoclonal antibodies taught by Mehta et al. do not render the particular protein of the claimed invention obvious. Mehta et al. neither disclose, nor suggest, the particular protein of the claimed invention. The Examiner provides no arguments otherwise, and instead, apparently relies on a faulty interpretation of the term "variant." Applicant respectfully requests that the rejection of claim 17, under § 103, be withdrawn.

Claims 2-3 were rejected under § 103(a) as allegedly being obvious over Minutello et al. in view of Rowlands et al. The Examiner asserted that Minutello et al. teach that HCV antigens stimulate proliferation of T and B lymphocytes specific for HCV proteins *in vivo* and that Rowlands et al. teach that T and B cells have a number of surface proteins of varying molecular weight, including proteins of approximately 24kd. The rejection concludes that the art teaches a T cell which binds HCV comprises the claimed protein, or its functional equivalent. Applicant respectfully traverses this rejection and submits that the claims are not obvious over Minutello et al. in view of Rowlands et al. Though claims 2 and 3 as amended are directed to a process, applicant will nonetheless address the Examiner's rejection.

The Examiner bases the obviousness rejection on the combined teachings of the cited art. In order to establish a prima facie case of obviousness, three basic criteria must be met: 1) there must be some motivation to modify the reference or to combine reference teachings; 2) there must be reasonable expectation of success; and 3) the reference or references must teach all of the

claim limitations. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). The Examiner has failed to meet this burden. Instead, using improper hindsight, the Examiner relies on the applicant's invention as a blueprint to combine and transform the cited art. *See In re Fritch*, 23 U.S.P.Q.2d 1780, 1784 (Fed. Cir. 1992) ("[i]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious").

Though Rowlands et al. report that T and B cells comprise a CD3 antigen of 25kd, nothing in Rowlands et al. suggests that CD3 is effective for binding HCV. Indeed, Rowlands et al. teach that CD3 is involved in the activation of protein kinase C during immune response by T cells. Minutello et al. do not overcome this deficiency. Minutello et al. do not disclose that CD3 is specific for HCV antigens. In fact, Minutello et al. do not discuss CD3 at all. Instead, Minutello et al. disclose that CD4 and CD8 bind HCV antigens. However, CD4 and CD8 are 55kd and 32/43kd, respectively. Minutello et al. do not disclose or suggest that the 25kd CD3 of Rowlands et al. binds HCV.

Even if motivation to combine Rowlands et al. and Minutello et al. existed, which applicant asserts it does not, the combination does not render obvious applicant's invention. The applicant's invention is a 24kd protein, or functionally equivalent variants or fragments thereof, which specifically binds to HCV. Conversely, the protein of Rowlands, CD3, is 25kd, and is taught to be involved in enzyme activation. The combined teachings of the cited art, therefore, do not yield a 24kd protein that binds HCV. This combination is an inappropriate application of hindsight. Applicant respectfully requests that the rejection of claim 1-3, under § 103, be

withdrawn.

Claims 4, 6-8, and 17 were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Minutello et al. in view of Rowlands et al., and further in view of Shimonaka et al. The Examiner argued that the combined teachings of Minutello et al. and Rowlands et al., as applied to claims 2-3, are equally applicable as to these claims.

Shimonaka et al., which purportedly discloses ammonium sulfate precipitation and HIC procedures, does not address or overcome the deficiencies discussed above with regard to Rowlands et al. and Minutello et al. As discussed above, discussion incorporated herein, there is no motivation to combine the references, and, if there were, the references would nonetheless not render obvious the claimed invention. Applicant respectfully requests that the rejection of claim 4, 6-8, 10 and 17, under § 103, be withdrawn.

Claims 4, 6-10, and 17 were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Minutello et al. in view of Rowlands et al., and further in view of Maat et al. The Examiner argued that the combined teachings of Minutello et al. and Rowlands et al., as applied to claims 1-3, are equally applicable to these claims.

Maat et al., which purportedly discloses acetone and ammonium sulfate precipitations, and HIC, does not address or overcome the deficiencies discussed above with regard to Rowlands et al. and Minutello et al. As discussed above, discussion incorporated herein, there is no motivation to combine the references, and, if there were, the references would nonetheless not render obvious the claimed invention. Applicant respectfully requests that the rejection of claim 4, 6-10 and 17, under § 103, be withdrawn.

CONCLUSION

For the foregoing reasons, the applicant requests that claims 2-4, 6-14, and 17 be allowed at this time. A notice of allowance is earnestly solicited.

Respectfully submitted,

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